LETTERS TO THE EDITOR

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Asymmetry and Vitalism.

IN your issue of September 22, Prof. Pearson, referring to the views expounded by Prof. Japp in his interesting address on "Stereochemistry and Vitalism," shows that, if chance be the only factor at work in the replacement of asymmetrical groups in symmetrical molecules, the production in nature of an excess, however small, of compounds of one-sided asymmetry must undoubtedly have taken place. But, ignoring the mechanical interpretation of the phenomenon (thus avoiding the stumbling-block hinted at by Prof. Pearson), and taking, according to present experience, for granted that, in the artificial introduction of asymmetry into a symmetrical compound, equal amounts of two inversely-active bodies are formed, so as to give rise to an optically inactive mixture or compound (in a way recalling to mind the separation of equal and corresponding amounts of positive and negative electricity), other objections may, in my opinion, be brought against Prof. Japp's views.

The point at issue is this: out of inactive material, vegetal and animal organisms are building up substances with asymmetrical molecules, and optically-active, such as albumins and carbohydrates. In which fact, joined with the chemists' then ascertained inability to prepare artificial active compounds from inactive substances, Pasteur saw an essential difference between the forces that are acting in living nature and such as are coming into play in our laboratories; he called, accordingly, the former asymmetrical, the latter symmetrical forces. This alleged barrier fell to the ground after the successful preparation, by Perkin and Duppa and by Jungfleisch, of racemic acid from succinic acid, and the separation, by means of a simple crystallising process, of sodium ammonium racemate into dextro- and lævo-tartrate, differing by their inverse hemihedral faces, and mechanically separable from one another. Being aware that the spontaneous separation of racemic acid into its two active forms afforded a strong argument against his theory, Pasteur uttered the belief that, even in that phenomenon, some asymmetrical outward agent, such as the organic germs contained in the atmosphere, might be the separating cause; but that hypothesis, inadequately supported by Joubert and Bichat with the doubtful evidence afforded by their experiments, cannot hold its ground against the facts discovered by Scacchi and Wyrouboff, and especially by Van 't Hoff and Deventer, respecting the so-called "transition-point" of some double salts, a class of compounds among which the racemates are but a particular case.

On Prof. Japp's view the asymmetrical forces are brought into play in another way and at another moment than on Pasteur's. He contends that, while simple asymmetry (exemplified by dextrotartaric or lævotartaric acid) is caused by asymmetrical actions, double asymmetry, as displayed by racemic acid, is caused by symmetrical actions: no asymmetry comes into play in the latter case, not even when the racemate is separating into its two enantiomorphs, as for every right-handed crystal a corresponding left-handed one is formed. But here is the point. When "the two kinds of crystals are to be picked out, and placed each in a vessel by itself," the intervention of an intelligent force, the intelligent and living (whether mediate or immediate) act of man is needed, as, both kinds having the same solubility, specific gravity, melting point, &c., behave in the same way towards all the separating symmetrical and non-living agents we dispose of in our laboratories. The conscious separation, carried out by man, may be compared with the unconscious one caused by bacteria and moulds, which agents are also able to destroy one kind rather than the other: the common side of both actions is that they are brought about by living organisms, formed of asymmetrical material, and therefore able to act asymmetrically.

Now, granting that, according to Prof. Japp's interpretation of facts, intervention of life cannot be dispensed with in the above separation, I believe that, supposing no substance endowed with molecular asymmetry to exist on our planet, it would be, not merely conceivable, but actually possible to produce as much simple asymmetry as might be desired, by means of an amount of one racemic compound (such as some racemate) liable to separation into active kinds, by the crystallising process, without any interfering asymmetrical force. In point of fact, after the spontaneous separation (the suitable temperature being granted) into the enantiomorphous crystals, we may always imagine a force, neither intelligent nor living, and acting in a symmetrical way, that would by chance single out *one* crystal: from that single, asymmetrical crystal (whether right- or left-handed), as was shown among other similar instances by Fischer and Wallach, other compounds can, on introducing asymmetrical groups, be prepared, displaying (without any previous separation into enantiomorphs) *simple* asymmetry. For, while a racemic compound always comes into existence when we start the synthetic process with a symmetrical and therefore inactive substance, such is not the case when we are operating on active, already asymmetrical compounds, as one active kind rather than its enantiomorph (with respect to the newly-introduced group) may be formed, the other one being partially or totally excluded. The pre-existing asymmetry has a directing influence upon the newly added atoms: asymmetry begets asymmetry, as life begets life. This argument does not only fit the hypothesis that a single crystal be selected: provided that the supposed force act for so short a time as to allow but a small part of the crystals to be removed, there is some chance for there being an excess, however small, of either one or the other enantiomorph to which the above remarks may as well apply.

The following illustration may perhaps convey a clearer idea of the fact stated. Supposing molecular asymmetry to have come on to our planet from outward space (an origin ascribed by some to life), let us imagine one primordial racemic compound to have spontaneously separated into its two enantiomorphs, and these to have been whirled round and scattered about vacant space by some vortex, so as to allow one simply asymmetrical particle to reach our globe. This may, without the intervention of any peculiar force differing at all from such as are acting in chemical synthesis, have originated all the now existent asymmetrical compounds. Some other planet might nevertheless have been reached by a particle of the other enantiomorph; the ensuing molecular asymmetry would accordingly have been the perfect reverse of ours: that celestial body might be inhabited by living creatures akin to ourselves, but built up of dextrogyrous albumins; its vine-grapes would yield *l*-glucose instead of *d*-glucose, &c. I do not mean to contend that there is any probability of such events having taken place, and am only pointing out that such an hypothesis is in no way absurd or inconceivable. Nay, it might even be enlarged. Although unlikely, a universe (in which our planet might well be included) can be imagined, being formed by pairs of celestial bodies endowed with equal and inverse asymmetry, so as to be comparable with a set of enantiomorphous crystals, into which a mixture of racemous compounds would separate. It matters little whether the enantiomorphs be near one another, as in the case of a crystallising solution, or as wide apart as the celestial bodies we are considering: there is in both cases *in a determinate point of space* one kind of simple asymmetry (the other one being excluded), a result attained without any absolutely asymmetrical action, and especially life, coming into play.

That the way followed by living organisms in their preparation of active substances, differs from the processes carried on in laboratories, is quite another question: the capital point is that, in one way as in the other, the final result is the same, and that the formation of the first asymmetrical group is not necessarily connected with that of the first living particle, as Prof. Japp contends. In my opinion, the problem of spontaneous generation is not likely to be ever reduced to the far simpler question of the origin of molecular asymmetry.

Turin, October. GIORGIO ERRERA.

I WILL endeavour to reply to the various criticisms which have appeared in NATURE on my address to the Chemical Section of the British Association.

Prof. Karl Pearson points out—what was, of course, obvious—that if only a small number of asymmetric molecules—say twenty—were to be formed under the influence of symmetric forces, there might be a preponderance of either right- or left-handed enantiomorphs, or even that all might be of one kind. He then goes on to suggest that such asymmetric compounds might have been spontaneously formed in the past, and might "be endowed with a power of selecting their own asymmetry from other racemoid compounds," and might thus act as "breeders."

This is a view which, as I have found in private discussion, is held by several organic chemists. My reason for rejecting it is that it attributes to the "breeding" process (to employ Prof. Pearson's concise, but, as we shall see, not altogether accurate expression) an efficiency which experiment does not justify. I will explain this important point in detail, as those who appeal to the "breeding" process seem to me to do so in a somewhat vague and elastic way.

This influence of already existing asymmetric molecules, or of asymmetric groups within the molecule, manifests itself in two ways, which I will distinguish as *asymmetric induction* and *asymmetric selection*.

(1) *Asymmetric Induction.*—If we introduce into an asymmetric molecule a fresh asymmetric carbon atom, or if we render asymmetric a carbon atom which was not previously so, the asymmetry already present will influence the character of the new asymmetry, and of the two possible arrangements of the new asymmetric carbon atom, one will predominate, or may even be the sole form. This influence, however, is entirely *intra*molecular; all attempts to convert asymmetric induction into an *inter*molecular action have failed. Thus various attempts have been made to obtain an optically active substance by allowing a reaction which under symmetric conditions would yield a racemoid mixture, to proceed in a solution containing another optically active substance; but this dissolved substance was invariably found to be without influence on the course of the reaction, and the resulting product was optically inactive. This influence, therefore, so far as experiment goes, does not extend from molecule to molecule, although within the molecule it is very powerful.

If the protoplasmic theory of vital synthesis is correct, according to which the molecules of carbon dioxide and other non-living molecules first combine with the living protoplasm and are afterwards eliminated in the form of asymmetric compounds, this asymmetric induction probably determines the asymmetry of the resulting compounds. But even supposing living protoplasm to consist of molecules—of which we have no proof—such molecules exercise their peculiar synthetic functions only under the influence of life, and are, therefore, useless as "breeders" for the purposes of Prof. Pearson's argument. Prof. Pearson's twenty non-living asymmetric molecules, formed by the chance play of mechanical forces, would, so far as experiment informs us—although I freely admit that mere negative results are not conclusive—have no more influence on the asymmetry of other molecules formed in their neighbourhood than one toss of a coin has upon another toss.

(2) *Asymmetric Selection.*—This is of two kinds. The first is that discovered by Pasteur, in which the different degree of affinity of one asymmetric base for two enantiomorphous acids (or of one asymmetric acid for two enantiomorphous bases) comes into play, and a separation may be effected, depending on the different solubilities of the resulting salts. But how this process would be available for Prof. Pearson's purpose, one hardly sees. In the most favourable case, his twenty asymmetric molecules would combine with a limited number—twenty, or some simple multiple or sub-multiple of twenty—of molecules from some racemoid mixture that happened to be present, and there would be an end of their action. There is no question of "breeding" here. Their number would not be increased by the process.

The other kind of asymmetric selection, which is a modification of that described by Pasteur, was discovered by Kipping and Pope. It depends on the fact that certain asymmetric substances, when in solution, alter in a different degree the solubility of two enantiomorphs, without actually, as in the previous case, entering into definite chemical combination with them. In this way a partial separation of enantiomorphs may sometimes be effected. But the applications of the method are very limited. Thus Kipping and Pope found that whilst, by means of a concentrated solution of glucose, they could effect a partial separation of sodium ammonium dextro- and laevo-tartrates—substances which spontaneously crystallise separately (*i.e.* not in racemic combination) at ordinary temperatures—in the case of mandelic acid, which is racemic at ordinary temperatures, no separation was effected, the tendency to form a solid racemoid overcoming any tendency to separation due to the presence of the glucose. Moreover, this action has never been observed, except with concentrated solutions of the selective substance; and it is, therefore, quite impossible that Prof. Pearson's twenty molecules—doubtless in a state of unlimited dilution—could in any way influence the solubility of other substances present.

My contention with regard to this "breeding" question, so far as non-living matter is concerned, therefore is: Asymmetric induction "breeds" only within the molecule, and without thereby adding to the number of molecules; asymmetric selection does not "breed" at all.

In fact, I do not see what Prof. Pearson is to do with his twenty molecules when he has got them. They will not "breed" in the sense he contemplates. On the other hand, if the process which produced them should go further, so as to yield a sensible quantity of substance, both enantiomorphs must be formed; and as the chances are equal in favour of the two asymmetric events; as, moreover, the occurrence of either event does not influence that of the other; and as the number of molecules in a sensible quantity is very great, Le Bel's ratio,

$$\frac{\text{Number of occurrences of event I.}}{\text{Number of occurrences of event II.}}$$

will not differ sensibly from unity.

Several of my critics seem to think that a mere sensible preponderance of one enantiomorph is sufficient. This is not the case unless the minority can be "bred" out of existence; and I do not think that under symmetrical conditions this is possible. We must bear in mind that, in the case of at least 99 per cent. of those optically active compounds which are products of the living organism, only one enantiomorph is found. It is the total disappearance of the opposite form which we have to explain.

Prof. Pearson, referring to the hypothesis of the asymmetric carbon atom, says: "Such a *geometrical* hypothesis cannot give the *dynamical* explanation of rotatory polarisation required by the physicist." Every chemist, of course, fully recognises this; and in addressing an audience of chemists, I did not think it necessary to introduce so obvious a qualification of my statements. In the present undeveloped state of stereochemistry we are compelled provisionally to treat, as statical, problems which are in reality dynamical. The atoms are considered as being at rest in the positions of equilibrium about which they actually oscillate or revolve. Or, as Van 't Hoff puts it, the problems of stereochemistry are tacitly treated in the form in which they might be conceived to present themselves at the absolute zero of temperature.

Prof. Fitzgerald makes two suggestions, either of which, he considers, would dispose of my contention that single asymmetric forms cannot arise under chance conditions. In the first of these he supposes a mixture of two enantiomorphs to separate spontaneously into its right- and left-handed crystalline forms. If life then started from a few such centres, there would probably be a preponderance of one or the other form; "if it started from a single centre, it *must* have been either right- or left-handed."

In reply I would point out that this spontaneous separation of enantiomorphs is confined to crystalline substances; and I should have thought it fairly obvious that crystalline substances cannot possibly form the organic structural material of living organisms. Can Prof. Fitzgerald imagine crystallised protoplasm?

Prof. Fitzgerald's second suggestion is that life "probably started either in the northern or in the southern hemisphere, and in either case the rotation of the sun in the heavens may be a sufficient cause for a right- or left-handed structure in an organism growing under its influence."

In attributing the origin of the molecular asymmetry of compounds produced in the living organism to the apparent diurnal motion of the sun, Prof. Fitzgerald has been anticipated by Pasteur. I had, therefore, carefully considered the question before writing my address. I do not assign any importance to the negative result of the experiment which Pasteur made with the object of detecting such an influence. Indeed, we need not consider Pasteur's experiment at all, inasmuch as nature has been carrying out for us on this very point an experiment of a similar character which has lasted from the first appearance of life on our planet to the present day—and has equally yielded a negative result. For, if this supposed influence were at work, the asymmetric compounds of vegetable origin produced in the northern and southern hemispheres respectively ought to display

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[1] Prof. Pearson waives any objections to my reasoning "arising from the fact that it is based on a purely geometrical hypothesis as to the constitution of molecules," &c. But even if Prof. Pearson feels inclined to put forward these objections, he will find that I point out, towards the close of my address, that the reasoning is independent of this hypothesis, and that it holds good equally of the hemihedral crystalline forms of these asymmetric compounds about which there is no hypothesis at all.

asymmetry in opposite senses. But nothing of the kind is observed. Cellulose, starch, saccharose, have the same right-handed asymmetry, each in its particular degree, whether the plant that produces them grows north or south of the equator.

Mr. Bartrum suggests that two enantiomorphs may crystallise from their equimolecular mixture with an unequal distribution of the right and left crystals; that then partial re-solution may occur, "roughly on the lines of the distribution of the two varieties of crystals," giving an optically active solution. Unlike Prof. Fitzgerald, Mr. Bartrum does not propose to vivify this crystalline substance offhand; he merely suggests that it may have been "the first ancestor of lævo-rotatory protein."

This is vague. As far as I follow its meaning I should read it: "Leave a soluble, crystallisable, asymmetric organic compound, of suitable character and composition, which has been formed and separated by the chance play of mechanical forces, long enough exposed to the action of other matter under the influence of these forces, and it will, in due course, first turn into protein and then come to life." I do not think that this statement misrepresents Mr. Bartrum's position, and I will leave it to speak for itself.

Mr. Bartrum's process of separation is also open to the objection that it would at best yield only an optically active *mixture—i.e.* with a mere preponderance of one enantiomorph; and as I have already pointed out, that is not a solution of the problem.

Mr. Herbert Spencer considers that I have ignored a universal law of "segregation" which he formulated in 1862 in his "First Principles," and which he there referred to three "abstract propositions" now quoted by him. He asserts that this law of segregation would account for the separation of dextro-protein and lævo-protein, if these were once formed; and he instances the formation of hæmatite nodules and flints in chalk-formations as an illustration of the power of segregation in nature.

I think that Mr. Spencer does not quite realise to what extent enantiomorphous molecules are alike. Every symmetric form of energy (such as heat), and every symmetric material agent, is identical in its action upon two enantiomorphs: whatever happens to the one happens to the other. And in none of these facts is there the slightest violation of the law of the conservation of energy—although Mr. Spencer's corollary to his third proposition would suggest the contrary. As regards the separation of enantiomorphs, I do not know whether Mr. Spencer would interpret his third proposition to mean that they must be separable by diffusion; but from the foregoing illustration which he gives of segregation in the inorganic world he would seem to have some such process in his mind. In that case I may point out that, as indeed follows from what I have already said, the rate of diffusion of enantiomorphs is the same; no such separation is possible.

If Mr. Spencer will consider this absolutely identical behaviour of enantiomorphs under all symmetric influences, I think he will perceive that the phenomena of "the formation of hæmatite nodules and flints in chalk-formations, or of siliceous concretions in limestone"—phenomena in which only crystalline or crypto-crystalline compounds of symmetric molecular structure are concerned, and which occur under the influence of symmetric forces—are not comparable with the separation of two enantiomorphous colloids such as dextro-protein and lævo-protein. Short of some asymmetric influence, nothing could separate these; and I am still waiting for my critics to tell me where, prior to the existence of life, such an influence was to be found.

Prof. Errera writes with special knowledge of the subject of molecular asymmetry, and I have nothing to criticise in his statements, so far as they deal with known fact or accepted theory. Some of his suggestions are exceedingly ingenious. I must admit, for example, that a force neither intelligent nor living—a symmetric mechanism—might be conceived which would pick out a *single* crystal from a mixture of crystallised enantiomorphs, and thus yield a single asymmetric compound. This is, then, so far a solution of the problem, although not a solution in the sense which I contemplated, since the mechanism cannot be trusted to effect the separation of the same asymmetric form twice running, whereas the living organism, or the intelligent operator, can do so any number of times. This is the essential difference between symmetric chance and asymmetric life. It is a feat which no mechanism could perform, unless its constructor had first embodied in it the idea of asymmetry, when it would cease to be symmetric, and would be an asymmetric product of living intelligence.

Moreover, as Prof. Errera will perceive from my reply to the arguments of Prof. Fitzgerald and Mr. Bartrum, I do not consider that the separation of enantiomorphous *crystals* brings us much nearer to the spontaneous formation of those *non-crystalline* asymmetric substances that build up the living organism. Prof. Errera, it is true, goes a step further in this direction than my other critics by pointing out that—as indeed I emphasised in my address—the further chemical transformation of such an asymmetric compound by the introduction of new asymmetric groups need not yield more than a single asymmetric compound.

Prof. Errera admits that his suggestions as to the manner in which the separation of enantiomorphs may have occurred before the origin of life—thus, that different asymmetric crystals may have been whirled by a vortex into different planets—are not very probable. In fact, all my critics seem to be moving in that unreal world where a fount of type, if jumbled together sufficiently often, ends by setting up the text of *Hamlet*.

In conclusion, I repeat that it is the impossibility of any mechanical (symmetric) force *constantly* producing the same asymmetric form, or *constantly* selecting the same one of two opposite asymmetric forms—a constancy which is manifest in the same processes when effected by vital agency—to which I referred in my address. I certainly nowhere used the word "constantly"; but the idea is present throughout.

Most of my critics clearly recognise this impossibility, and therefore seek to avoid the difficulty by supposing only a few asymmetric events—or even, only a single asymmetric event—to occur. The desired result having been obtained, the initial process is assumed to stop. But in making this assumption they seem to me to do violence to all probability. Given a practically unlimited period of time, why should a particular set of mechanical conditions, acting by pure chance in a given way, not act over and over again? One can understand a gambler stopping after a run of luck in his favour; but why should a mechanical process do so?

I see no reason to withdraw any of the conclusions at which I arrived, although, had I to write my address over again, there are parts which, to guard against misunderstanding, I might express differently.

I wish to point out that the term "tetartohedral," used in my printed address in describing the asymmetric facets of quartz, is erroneously given in the NATURE report (this vol., p. 454, col. 1) as "tetrahedral."

F. R. JAPP.

The University, Aberdeen, October 24.

Potential Matter.

ALLOW me to refer once more to the subject of my letter of August 18, in order to draw attention to two previous investigations with which, at the time of writing, I was unacquainted. Prof. Karl Pearson has, under the title of "Ether Squirts" (*American Journal of Mathematics*, vol. xiii. No. 4), worked out mathematically the theory of matter considered as sources and sinks of fluid, and draws attention to the fact that this theory implies the existence of "negative matter," which may exist outside the solar system. More recently A. Föppl, in a communication to the Munich Academy, dated February 1, 1897 (*Sitzungsber. der k. b. Akad. d. Wiss.*, 1897, i. p. 93), has published a short paper under the title, "Ueber eine mögliche Erweiterung des Newton'schen Gravitations-Gesetzes." Starting from the idea that there is a difference in kind between the electrical and magnetic fields of force on the one hand, and the gravitational field on the other, because the flux of force through a sphere converges towards zero with increasing radius of the sphere for the electric and magnetic fields, but not, as usually defined, for the gravitational field, Föppl gives the necessary extension to Newtonian law of gravitation in order to remove the distinction. This, of course, implies "negative matter." There is a marked difference between the expression for the energy of the gravitational field on Föppl's hypothesis with that which is derived from the ether squirt theory; but it is not necessary to enter into this question.

There are some points in my former communication, to which previous writers on the subject have, however, not, as far as I know, drawn attention. Among them is the insufficiency of the ordinary hypothesis to account for the rotational momentum